PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61L 25/00 — A1

(11) International Publication Number: WO 93/01841

(43) International Publication Date: 4 February 1993 (04.02.93)

(21) International Application Number: PCT/EP92/01619

(22) International Filing Date: 16 July 1992 (16.07.92)

(30) Priority data:
9115901.2 23 July 1991 (23.07.91) GB

(71)(72) Applicants and Inventors: BRADNOCK, Brian, R., D., P. [GB/GB]; 39 Blackford Road, Edinburgh EH9 2DT (GB). LAW, Hamish, Turner [GB/GB]; 8 Learmonth Terrace, Edinburgh EH4 1PQ (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).

Published
*With international search report.*

(54) Title: IMPROVEMENTS IN ANTIBIOTIC-CONTAINING ACRYLIC BEADS

(57) Abstract

Implanted small spheres of polymethyl methacrylate (PMMA) bone cement ("beads") containing antibiotics have been used to provide prophylactic cover following orthopaedic surgical procedures or in the treatment of bone infections. The choice of antibiotic is restricted by the temperature of the exothermic polymerisation reaction, which is damaging to many of the antibiotic agents which would otherwise be useful. By carrying out the polymerisation in two stages and providing means of cooling during the first the maximum temperature to which the therapeutic agent is exposed is substantially reduced, thus avoiding thermal damage. Similar considerations apply also, for example, to the use of anti-tuberculous drugs and chemotherapeutic agents for the treatment of tumour in bone, many of which are heat sensitive. These may be incorporated in the modified PMMA bead.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|---|---|---|---|---|---|
| AT | Austria | FI | Finland | ML | Mali |
| AU | Australia | FR | France | MN | Mongolia |
| BB | Barbados | GA | Gabon | MR | Mauritania |
| BE | Belgium | GB | United Kingdom | MW | Malawi |
| BF | Burkina Faso | GN | Guinea | NL | Netherlands |
| BG | Bulgaria | GR | Greece | NO | Norway |
| BJ | Benin | HU | Hungary | PL | Poland |
| BR | Brazil | IE | Ireland | RO | Romania |
| CA | Canada | IT | Italy | RU | Russian Federation |
| CF | Central African Republic | JP | Japan | SD | Sudan |
| CG | Congo | KP | Democratic People's Republic of Korea | SE | Sweden |
| CH | Switzerland | | | SN | Senegal |
| CI | Côte d'Ivoire | KR | Republic of Korea | SU | Soviet Union |
| CM | Cameroon | LI | Liechtenstein | TD | Chad |
| CS | Czechoslovakia | LK | Sri Lanka | TG | Togo |
| DE | Germany | LU | Luxembourg | US | United States of America |
| DK | Denmark | MC | Monaco | | |
| ES | Spain | MG | Madagascar | | |

# IMPROVEMENTS IN ANTIBIOTIC-CONTAINING ACRYLIC BEADS

This invention relates to orthopaedics and to improvements in the design of polymethyl methacrylate (PMMA) beads containing admixed antibiotic or other therapeutic agents.

Antibiotic-containing PMMA beads are intended for implantation within the body at the time of operation during orthopaedic surgical procedures in order to provide prophylactic post-operative antibiotic cover, or may be used in the treatment of deep infections involving bone. Deep infection following bone or joint surgery is a known complication of such procedures with an incidence of about 1.5 percent. In joint replacement surgery it is the cause of a small but significant proportion of failures, usually requiring the removal of the prosthetic components to allow effective treatment of the infected bone. In non-surgical cases osteomyelitis may be caused by staphyloccocal infection, perhaps by haematogenous spead from some superficial infected site or following trauma, by salmonella, tuberculosis or other organisms. These are serious conditions requiring careful management. Antibiotics administered systemically are not very effective in the treatment because of the relatively sparse blood perfusion in bone and, consequently, the low concentration of antibiotic obtained at the site of the infection.

Previous workers have suggested the admixture of quantities of suitable antibiotic with the "bone cement" commonly used in modern orthopaedic surgery to attach prosthetic components to bone. The bone cement is an acrylic resin (polymethyl methacrylate, abbreviated PMMA) which is usually supplied for use

in the operating theatre in a two component form, a powder, consisting of small granules of partially polymerised methacrylate, and a liquid, consisting mainly of monomeric methyl methacrylate but containing also a catalyst and other agents which serve to promote a further polymerisation reaction during "curing". The powder and liquid are mixed together in theatre immediately before the cement is required for use. The mixture assumes the consistency of a thick "dough" one or two minutes after mixing and is applied to the bone and/or prosthetic components in this condition. Within ten minutes or so the mixture has set into a hard, solid mass effectively anchoring the prosthetic component to the bone. Antibiotics, in the form of dry powders, can be added to the bone cement at the time of mixing and become dispersed and embedded in the cured PMMA mass. The cement is slightly porous and permeable to water and water-soluble molecules so that the antibiotic slowly diffuses out from the solid cement and into the surrounding tissues, thus maintaining high bactericidal concentrations at and near the operation site.

Some of the commercially-produced formulations of bone cement contain inorganic materials to render the cement more opaque to x-rays and thus to help visualise the shape and extent of the cement mantle on post-operative x-ray examination. Barium sulphate or zirconium dioxide are two compounds which are commonly used. It has been shown that the presence of these inorganic additives greatly increases the diffusion coefficient of water soluble molecules in the cement. Almost all antibiotic therapy with PMMA-dispensed agents is based on the use of radio-opaque bone cement formulations, since the rate of drug delivery from PMMA with no inorganic additive is usually too low.

As a variation of these techniques antibiotic-containing PMMA beads have

become commercially available, usually in the form of "chains" threaded on a flexible stainless steel wire. These are used in the treatment of bone infections and can be packed into the space resulting from surgical removal of infected or damaged bone or within the medullary cavity of long bones. These chained beads may be removed after the infection has been brought under control thus minimising needless and undesirable exposure to continuing dosage of antibiotic which carries the risk of the development of antibiotic-resistant organisms. In this variation the PMMA is used solely as a vehicle for the antibiotic and, since it is not required to provide a strong means of attachment for a prosthetic component, its mechanical properties are not important. High concentrations of antibiotic (which impair the mechanical properties of the cured cement) may therefore be used. Antibiotic-containing beads are most usually pre-manufactured and delivered to the theatre in sterile packs ready for use.

The polymerisation reaction is exothermic, thus the temperature of the cement rises during the curing process. The maximum temperature attained will depend on the thickness of the cement mantle, the proximity of metallic prosthetic components and so on. The temperature at the centre of a ball of cement several centimetres in diameter will reach approximately 120 degrees Centigrade during the curing process and sections only two millimetres thick will exceed 80 degrees Centigrade. Many of the antibiotics which are suitable for use prophylactically or therapeutically in the control of deep infections involving bone are unstable at these temperatures and are therefore rendered ineffective during the cement polymerisation reaction.

The purpose of the present invention is to provide a method of manufacturing antibiotic-containing PMMA beads which avoids exposure of the antibiotic to damaging temperatures. As a consequence, it becomes possible to use some antibiotics which are known to be effective in the treatment of deep infection of bone but which would lose their bactericidal properties, in whole or in part, as a result of the high curing temperature of PMMA beads of conventional design. A wider choice of antibiotic is available in the treatment of the infection, an important consideration when the infecting organisms are found on testing to be resistant to the more commonly used antibiotic agents.

A specific embodiment of the invention will now be described by way of example. The PMMA powder and the required quantity of antibiotic, or combination of antibiotics, are thoroughly mixed after which the liquid monomeric methyl methacrylate with catalyst and accelerators is added and stirred in. Immediately thereafter the mixture is spread on a thin sheet of stainless steel or other suitable metal and second such sheet is placed on top so as to form a metal/cement mix/metal "sandwich". The sandwich is fed between successive pairs of cylindrical metal rollers of progressively decreasing spacing so as to reduce the spacing between the two metal sheets, and thus the thickness of the cement layer between, to the required value, which is in the order of 0.2 millimetres. Bumps or other raised areas may be formed on one or other of the metal sheets to control the separation between them during the rolling process. These operations must be completed before the polymerisation reaction has progressed more than a few percent but this does not present a difficulty.

The rolled-down sandwich is then set aside to allow the cement to cure. Because of the thin section of cement, in contact on each side with the metal plates, the temperature rise during polymerisation is limited by the conduction of heat away from the polymer into the metal. In this way the maximum temperature which is attained may be limited to less than 10 Centigrade degrees above the ambient temperature. If a particularly heat-sensitive antibiotic is being used lower maximum temperatures may be obtained by providing means of cooling the plates, by working in a cooler environment or by using precooled materials, plates and rollers.

When curing is complete the cement is broken out from the containing plates and is then broken up by passing it through serrated rollers so as to produce granules. These are subsequently graded in size by means of sieves. The granule size has a considerable effect on the rate at which the antibiotic will be released, by diffusion, from the completed bead and in consequence the maximum size and the spectrum of sizes which are used in the later stages requires to be carefully controlled. As an aid to this description the maximum dimensions of the granules will most often be in the range 0.5 to 1.7 millimetres, although the invention is not restricted to this range of sizes.

During the final manufacture of the bead further small quantities of the monomeric methyl methacrylate and catalyst are added to the granular mix and the bead formed by moulding or other appropriate process. A hole for the wire on which the beads will be strung is formed at this stage. For illustration, the diameter of the completed beads will be, typically, between 10 and 20 millimetres. The granules are compacted and will become firmly bonded to each other at their points of contact as a result of further polymerisation which

takes place at these points. Though this reaction is again exothermic and some temperature rise will take place the quantity of reacting material is small, dependent mainly on the amount of liquid monomer which is added, and the maximum temperature attained is therefore acceptable.

The resulting bead has an open, porous structure with intergranular voids which are large compared to those found in conventionally prepared, cured PMMA. The mechanical strength is thus relatively low but this is of no consequence since the material is not required to be load-bearing. The porosity will considerably increase the rate of diffusion of the water soluble antibiotic molecules from the bead and into the surrounding tissues after implantation, which is advantageous. The diffusion rate can be adjusted to suit the pharmacological requirements by variation of the granule size (and size distribution) and, of course, by selection of the original antibiotic content.

PMMA beads of the form described above may be used with advantage to provide long duration, continuing delivery of therapeutic agents other than antibiotics. As examples, anti-tuberculous drugs and compounds used in chemotherapy for tumour may be incorporated. Many such agents are heat sensitive and thus unsuitable for incorporation into PMMA beads of "solid" design.

CLAIMS

1. A synthetic resin bead, containing one or more therapeutic agents, for implantation within the human body made by a two-stage polymerisation process, following incorporation of the therapeutic agent, which substantially reduces the maximum temperature attained during polymerisation by limiting the physical dimensions of the resin material during the first stage of polymerisation and providing means of cooling.

2. A synthetic resin bead as claimed in Claim 1 in which the first of the two stages of polymerisation produces a thin sheet of resin between two metal plates, which provide the means of cooling by conduction, the cured resin sheet being afterwards broken up to provide particles or granules of a known size distribution which are in a later stage agglomerated and interconnected using a small additional amount of monomer and catalyst to initiate the second stage of polymerisation.

3. A synthetic resin bead as claimed in Claim 1 or Claim 2 in which the therapeutic agent is an antibiotic, the bactericidal properties of which would be impaired or destroyed by exposure to elevated temperatures.

4. A synthetic resin bead as claimed in Claim 1 or Claim 2 in which the therapeutic agent is a anti-tuberculous drug.

5. A synthetic resin bead as claimed in Claim 1 or Claim 2 in which the therapeutic agent is one used in the treatment of tumour of bone, including metastatic tumour.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01619

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61L25/00

## II. FIELDS SEARCHED

**Minimum Documentation Searched[7]**

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | A61L |

**Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]**

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No.[13] |
|---|---|---|
| Y | GB,A,2 219 303 (TECRES SPA)<br>6 December 1989<br>see page 4, line 12 - line 21<br>see page 7, line 17 - line 29<br>see page 10, line 11 - line 17<br>see page 12, line 26 - line 30 | 1-5 |
| Y | EP,A,0 361 408 (WOLLF & KAABER A/S)<br>4 April 1990<br>see page 6, line 20 - line 24<br>see page 9, line 15 - line 18; claims | 1-5 |
| Y | US,A,4 554 686 (CHARLES D. BAKER)<br>26 November 1985<br>see column 4, line 15 - line 37<br>see column 5, line 18 - line 62; claims | 1-5 |

-/--

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 15 OCTOBER 1992 | 09. 11. 92 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT FFICE | M. ESPINOSA |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| A | WO,A,8 602 370 (FERRING LABORATORIES, INC.)<br>24 April 1986<br>see page 3, line 7 - line 20; claims | 1-5 |
| A | EP,A,0 111 759 (BEIERSDORF AKTIENGESELLSHAFT)<br>27 June 1984<br>see claims | 1-5 |
| A | DE,A,3 738 422 (BEIERSDORF AG)<br>24 May 1989 | |
| A | FR,A,2 638 972 (LES LABORATOIRES OSTEAL MEDICAL)<br>18 May 1990 | |
| A | JOURNAL OF BIOMEDICAL MATERIALS RESEARCH<br>vol. 20, 1986,<br>pages 839 - 852<br>G.M. BRAUER ET AL. 'DPENDENCE OF CURING TIME, PEAK TEMPERATURE, AND MECHANICAL PROPERTIES ON THE COMPOSITION OF BONE CEMENT' | |